Cytochrome P4501A2: Enzyme Induction and Genetic Control in Determining 4-Aminobiphenyl-hemoglobin Adduct Levels

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Abstract

Cytochrome P4501A2 (CYP1A2) activity may be related to bladder cancer risk through metabolic activation of aromatic amines, such as 4-aminobiphenyl (ABP), to reactive intermediates that can form DNA and hemoglobin (Hb) adducts. In the context of a study on smoking and bladder cancer risk, 97 healthy male smokers were investigated. CYP1A2-dependent N-oxidation activity was measured using a molar ratio of urinary caffeine metabolites [(paraxanthine + 1,7-dimethyluric acid)/caffeine] obtained between the fourth and fifth h after drinking a standardized cup of coffee. N-Oxidation activity was induced by blond tobacco smoke, meat consumption the dinner before the test, or more than four cups of coffee a day. The regular use of medication appeared associated with a decrease in N-oxidation levels. Age and alcohol consumption were not related with CYP1A2 activity.

A polymorphic distribution of the CYP1A2 and N-acetyltransferase-2 (determined by the caffeine metabolite ratio 5-acetylamino-6-formylamino-3-methyluracil:1-methylxanthine) phenotypes was examined in relation to susceptibility to ABP-Hb adduct formation. Rapid oxidizers and subjects with the combined slow acetylator-rapid oxidizer phenotype showed the highest ABP-Hb adduct levels at a low smoking dose. Blond tobacco smokers exhibited higher adduct levels compared with black tobacco smokers, after adjustment for the quantity of cigarettes smoked. At the highest levels of smoking exposure, no major difference in ABP-Hb adduct levels was found among the different combinations of CYP1A2 and N-acetyltransferase-2 phenotypes. In a subset of only 45 available samples, no association was seen between the ABP-Hb adduct levels and the glutathione S-transferase M1 genotype.

Introduction

CYP1A2 catalyzes the metabolism of many drugs and environmental toxins and is responsible for the metabolic activation of various carcinogens, such as aromatic amines (i.e., ABP) and heterocyclic amines (1). Large interindividual differences of hepatic CYP1A2-dependent N-oxidation activity have been found in humans and are considered the basis for genetically determined differences in susceptibility to cancer risk arising from aromatic amine exposure. However, this variability could also be due to exposure to concomitant unidentified enzyme inducers and/or different degrees of responsiveness to such inducers. No polymorphic sequences in the structural CYP1A2 gene that reflect interindividual differences in enzyme activity have been found yet (2). CYP1A2-related activity can be phenotypically measured by assessing caffeine metabolites in the urine (3–4), because caffeine is 3-demethylated by a CYP1A2-mediated reaction (5).

In the context of a study on smoking and bladder cancer risk, we have investigated in healthy male smokers and nonsmokers the factors that may influence CYP1A2-related activity and whether the level of ABP-Hb adducts is related to CYP1A2 phenotype.

ABP is a well-established bladder carcinogen in humans (6) and CYP1A2-mediated N-oxidation is a necessary pathway leading to reactive intermediates that form DNA and Hb adducts (7). The level of adducts may be a predictor of bladder cancer risk (8–9).

Previous studies have suggested that gender, age, and ethnicity may affect the phenotypic expression of CYP1A2 (10–11). To control for these inducing factors, we have studied a group of male Caucasians within a limited age range. In a previous study on this same population (12), we showed that ABP-Hb levels are associated with NAT2 phenotypes in a dose-related fashion; in particular, slow acetylator subjects showed the highest ABP-Hb levels in those who smoked little. Therefore, in this study, we examined ABP-Hb levels by combined acetylator and N-oxidizer phenotypes according to smoking levels. In addition, in 45 study subjects for whom data on GSTM1 genotype were available, the ABP-Hb levels by GSTM1 genotype and by combined CYP1A2 phenotype and GSTM1 genotype were also investigated.

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1 To whom requests for reprints should be addressed.

2 The abbreviations used are: CYP1A2, cytochrome P4501A2; ABP, 4-amino-biphenyl; Hb, hemoglobin; NAT2, N-acetyltransferase-2; GSTM1, glutathione S-transferase M1; NICO, nicotine + cotinine/creatinine; (17X + 17U)/17X; paraxanthine + 1,7-dimethylurea/caffeine; AFMU, 5-acetylamino-6-formylamino-3-methyluracil; 1X, 1-methylxanthine; PRR, prevalence rate ratio; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)1-butanone.
Materials and Methods

One hundred white, healthy, male volunteers between the ages of 45 and 64 were recruited in Turin, Italy. Fifty subjects were currently nonsmokers; 31 were blond (flue-cured) tobacco smokers; 16 were black (air-cured) tobacco smokers; and 3 were pipe smokers (excluded from the study). All subjects signed an informed consent form and responded to a questionnaire on smoking, coffee consumption, diet, occupation, medication use, and illness (demographic and other characteristics of study subjects are described in Table 1). Subjects were asked to avoid drinking coffee for 2 days prior to the study; then, on the morning of the interview, subjects provided 20-ml blood samples and urine samples between the fourth and fifth h after drinking a standardized cup of coffee. Blood components were shipped in dry ice to the Massachusetts Institute of Technology (S. T., P. S.) for ABP-Hb determination and to the National Cancer Institute (P. S.) for GSTM1 genotype analysis. Urine samples were shipped to the IARC (H. B., now at the German Cancer Research Center, and C. M.) for nicotine and cotinine measurements and to the National Center for Toxicological Research (F. K.) for CYP1A2 and NAT2 phenotype analyses. Urinary levels of NICO were measured as described previously (13) as an indicator of recent smoke exposure.

Caffeine and its metabolites were extracted from urine samples and analyzed by high-performance liquid chromatography, using a program that separated caffeine and all its known metabolites. The molar ratio of (17X + 17U)/137X, obtained between the 4th and 5th h after coffee consumption, was used as an index for CYP1A2-related enzyme activity (1). Probit analysis suggested the value of 4.6 as a cutoff point between rapid and slow oxidizers. Over the range of 20–60 ml urine/h, this metabolite ratio is independent of the urine flow rate and is closely correlated with results obtained using the caffeine breath test.3

The ratio of AFMU:1X was used to assign the acetylation phenotype (rapid acetylators, ≥0.6; slow acetylators, <0.6; Ref. 14).

Capillary gas chromatography with detection by negative-ion chemical ionization mass spectrometry was performed for quantification of ABP covalently bound as sulfenic acid amide to cysteine 93 of Hb (15). Results are expressed as pg ABP/g Hb.

The GSTM1 genotype was detected using a PCR-based method (16). Due to a shipping problem, only 45 samples were available for this analysis.

Univariate descriptive methods and ANOVA with the SAS statistical package (17) were used for statistical evaluation (18). PRRs and their 95% confidence intervals were calculated to compare the proportion of subjects with ABP-Hb greater than the median value in rapid versus slow N-oxidizers (19–20). The use of PRRs was deemed preferable, in accordance with many authors (19, 21–22), to the other commonly used estimator prevalence odds ratio, because when the outcome being investigated in cross-sectional studies (here, the proportion of subjects with ABP-Hb greater than the median value) is not rare, the odds ratio results in an inflated value away from 1.0.

Results

Some variables (i.e., ABP-Hb, N-oxidation activity, and GSTM1) were not normally distributed in the study population. Analyses with logarithmic and square root transformations did not appreciably vary the results. Thus, results of the analyses with nontransformed variables are reported here.

CYP1A2-related N-oxidation mean levels did not appreciably change when subjects were classified by increasing NICO levels (Table 2); neither did they show notable differences by increasing nicotine or cotinine levels analyzed separately (data not shown). When current smokers were classified as blond tobacco and black tobacco smokers, blond tobacco smokers showed higher N-oxidation activity than black tobacco smokers (Table 2). This difference was present despite a similar number of cigarettes smoked per day in the two groups and the fact that black tobacco smokers showed higher NICO levels than blond tobacco smokers (23). Among the nonsmokers, the 10 subjects exposed to passive smoke showed the highest N-oxidation activity. Two current smokers showed an extremely high level of N-oxidation activity (ratios of caffeine metabolites, 32.3 and 39.3 versus mean level, 4.7). All the variables tested with the intention of explaining these high values failed to show an association with N-oxidation activity. This finding appeared to be due to low urinary caffeine concentrations, which were near the detection limit and resulted in inflated values of (17X + 17U)/137X. Thus, we excluded these two subjects from all the analyses reported here.

In a two-way ANOVA with smoking (NICO or tobacco type) and expresso coffee consumption (four or less and more than four cups per day) as independent variables, coffee

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of study subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine + cotinine</td>
<td>0</td>
</tr>
<tr>
<td>n</td>
<td>40</td>
</tr>
<tr>
<td>Age range (yr)</td>
<td>43–63</td>
</tr>
<tr>
<td>≥4 coffee</td>
<td>11 (28)</td>
</tr>
<tr>
<td>Medication</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Meat</td>
<td>18 (45)</td>
</tr>
<tr>
<td>Wine</td>
<td>22 (55)</td>
</tr>
<tr>
<td>PAH</td>
<td>6 (15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>CYP1A2 activity by smoking exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>No. of subjects</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine + cotinine</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>25</td>
</tr>
<tr>
<td>1.5–2.4</td>
<td>9</td>
</tr>
<tr>
<td>2.5+</td>
<td>17</td>
</tr>
<tr>
<td>Smoking categories</td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>14</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>20</td>
</tr>
<tr>
<td>Passive smokers</td>
<td>10</td>
</tr>
<tr>
<td>Current smokers</td>
<td>45</td>
</tr>
<tr>
<td>Blond tobacco (22%)</td>
<td>30</td>
</tr>
<tr>
<td>Black tobacco (23%)</td>
<td>15</td>
</tr>
</tbody>
</table>

* (17X + 17U)/137X (urinary molar ratio of caffeine metabolites).
† Micromoles per nmol creatinine.
‡ Mean cigarettes per day.

3 Fred Radulski, personal communication.
drinking was related to a modest increase in N-oxidation activity, more evident in the model with NICO than in that with tobacco type. However, the small increase was not internally consistent in the different smoking strata.

Age, urine volume, and alcohol consumption did not show associations with N-oxidation activity (data not shown). Very few subjects were exposed to polycyclic aromatic hydrocarbons in the workplace (Table 1); this exposure was not related to CYP1A2 activity. No other occupational exposures resulted from the questionnaires.

Twenty-three subjects took medication regularly; they showed a decrease in enzyme activity (mean, 3.24; SD, 1.87) in comparison to both subjects who took medication only the day before the caffeine test (mean, 4.61; SD, 2.82; n = 59) and subjects who took no medication (mean, 4.83; SD, 2.78; n = 9; P = 0.09). The range of medications was very wide but did not include known inducers of CYP1A2 (24). One subject regularly took anticonvulsants and had N-oxidation activity of 2.3 and ABP-Hb of 13 pg/g Hb.

The 47 subjects who ate meat at dinner the day before the study showed higher N-oxidation activity (mean, 4.99; SD, 2.95) in comparison with subjects (n = 44) who ate no meat for dinner (mean, 3.54; SD, 2.08). The difference reached statistical significance (P = 0.008). Interestingly, the highest levels of N-oxidation activity were found in those subjects who ate grilled or charcoal-broiled meat, but further analyses were limited by the small number of these subjects (n = 3; mean, 8.77; SD, 3.53). However, N-oxidation was not associated either with meat consumption at lunch or at both lunch and dinner. Only three subjects ate cruciferous vegetables, such as broccoli or cabbage, at lunch the day before the study. Their N-oxidation activity was between 2.83 and 9.35.

In a previous study in the same cohort, probit analysis of the CYP1A2 phenotype showed an apparently trimodal (slow, intermediate, and rapid) distribution (1), but because there were very few subjects in the lowest category (n = 4), we simply dichotomized the distribution into slow and rapid phenotypes. A cutoff value for the caffeine metabolite ratio was identifiable in the range between 4.6 and 7.0. The value of 4.6 was used in all analyses reported here. The use of higher values within the 4.6-7.0 N-oxidation interval did not substantially alter our findings.

At increasing NICO levels, subjects with a slow oxidizer phenotype showed a monotonic increase in ABP-Hb, ranging from 31 to nearly 150 pg/g Hb (Table 3). A steep increase was also observed in subjects with a rapid phenotype; however, at the highest NICO level, the rapid-phenotype subjects failed to show a further increase in adduct levels. Thus, the major difference in adduct levels between rapid and slow oxidizers was evident at NICO <1.5 μmol/mmol creatinine. Similarly, in the analysis by tobacco type, rapid oxidizers showed the largest increase over slow oxidizers in ABP-Hb levels in blond tobacco smokers. In contrast, although limited by the low number of rapid oxidizers, black tobacco smokers showed a suggestive inverse pattern.

### Table 3: Comparison of ABP-Hb adduct levels by CYP1A2 activity and smoking exposure

<table>
<thead>
<tr>
<th>Exposure groups</th>
<th>CYP1A2 slow phenotype</th>
<th>CYP1A2 rapid phenotype</th>
<th>PRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>n</td>
</tr>
<tr>
<td>Nicotine + cotinine*</td>
<td>28</td>
<td>31.43 ± 24.43</td>
<td>10</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>16</td>
<td>62.25 ± 49.93</td>
<td>9</td>
</tr>
<tr>
<td>1.5+</td>
<td>14</td>
<td>149.71 ± 52.93</td>
<td>12</td>
</tr>
<tr>
<td>Smoking categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non smokers + ex-smokers</td>
<td>25</td>
<td>29.12 ± 22.58</td>
<td>7</td>
</tr>
<tr>
<td>Blond tobacco smokers (22‡)</td>
<td>13</td>
<td>87.23 ± 60.48</td>
<td>17</td>
</tr>
<tr>
<td>Black tobacco smokers (23‡)</td>
<td>12</td>
<td>154.41 ± 42.08</td>
<td>3</td>
</tr>
</tbody>
</table>

*Picograms per g hemoglobin.
‡(17X + 17U)/17X; cutoff point, 4.6.
‡Effect: ABP > 56 pg/g hemoglobin (median value). CI, confidence interval.
‡Micromoles per mmol creatinine.
‡Mean cigarettes per day.

**Discussion**

N-Oxidation activity was measured through the (17X + 17U)/17X caffeine urinary ratio, which was shown to better reflect the rate constant for the CYP1A2-catalyzed 3-demethylation of caffeine in vivo (1) than other previously reported ratios, i.e., 17X/137X (25), (AFMU + 1X + 1U)/17U (26), or (AAMU +...
1X + 1U)/17U (11). Others (27) have suggested that the ratio of (17X + 17U)/137X reflects only a polymorphism in renal clearance of 137X. We did not find this result and agree with Birkett and Miners (28) that urinary caffeine concentration is independent of urine flow rate. Instead, there is a urinary constituent that exhibits urine flow dependence and often comigrates with caffeine.4

\[ \text{ABP-Hb adducts by combination of CYPIA2 and NAT2 phenotypes and tobacco type. Adducts are expressed as pg ABP/g Hb; CYPIA2 and NAT2 phenotypes are calculated based on the urinary molar ratio of caffeine metabolites [(17X + 17U)/137X and AFMU/1X, respectively]; R, rapid; S, slow.} \]

\[ \text{Fig. 2.} \]

\[ \text{Fig. 1.} \]

\[ \text{N-Oxidation activity was found to be inducible by many substances. Based on the same number of cigarettes smoked, current blond tobacco smokers showed higher N-oxidation activity than black tobacco smokers. The search for possible inducers in blond tobacco is difficult, because cigarette smoke contains more than 3000 substances (29). Black tobacco smoke contains higher amounts of aromatic amines, but other compounds, such as the tobacco-specific nitrosamines NNK and/or N'-nitrosoanatabine, are twice as high in blond as in black tobacco (30). NNK, one of the most potent carcinogens contained in tobacco (mainly derived from nicotine during tobacco curing; Ref. 29), is known to be also metabolized by CYPIA2} \]

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N-oxidation activity than nonsmokers who were not exposed to cigarette smoke. Because the type of tobacco inhaled was unknown, we were unable to evaluate whether this increase was due to side-stream smoke in general or to blond tobacco side-stream smoke. Thus, all subjects who reported exposure to side-stream smoke in the questionnaire were excluded from the analysis by tobacco type.

Subjects who had more than four cups of coffee per day showed a slightly higher enzyme activity level. This finding confirms the results recently published by Horn et al. (33) and could be interpreted as due to the induction of N-oxidation activity by caffeine. However, this is more likely to be due to the fact that rapid oxidizers consume more coffee, probably because they metabolize it very quickly (34). In fact, several studies have shown that caffeine itself does not induce its own metabolism (35).

Overall, the N-oxidation ratio in our study subjects was lower than in other non-Italian populations. An ethnic difference in the constitutive expression of CYP1A2 and/or a relatively lower meat protein intake in the Italian diet might be the explanation. In this regard, the subjects who ate meat at dinner only the day before the caffeine test showed a higher level of N-oxidation activity. This finding is consistent with other studies that showed an induction of oxidative metabolism by high levels of dietary proteins (36). Although the sample size was small, the highest activity levels were found in three subjects who consumed charcoal-broiled or grilled meat. A possible induction of CYP1A2 activity by heterocyclic amines or polycyclic aromatic hydrocarbons formed during cooking procedures, in addition to the protein intake, has been suggested (37). Conversely, no induction was seen when meat was eaten at lunch on the day prior to the study. This is in accordance with animal data showing that maximal induction of CYP3 occurs after a period of 10–12 h (38), which corresponds in our study to the time elapsed between dinner and urine sample collection. However, the absence of an increase in N-oxidation activity in subjects who ate meat both at lunch and at dinner remains to be elucidated.

N-Oxidation activity was not associated with alcohol consumption. One explanation might be that in our study, only a very few subjects were beer drinkers, a group that exhibited a weak association with N-oxidation activity in a previous study (33).

Regular use of medication was associated with a decrease of N-oxidation activity, as reported previously (33). Subjects who took a large variety of drugs, and the analysis by single class of medication yielded limited information given the small sample size. One subject, who was an ex-smoker, regularly took antidepressants and showed an average N-oxidation level but one of the lowest ABP-Hb levels. A larger study is thus necessary to confirm the inverse relationship between phenobarbital use and ABP-Hb levels suggested previously (39).

N-Oxidation activity may also be genetically polymorphic in the population and may determine the variable human risk of tumors related to aromatic and heterocyclic amine exposure. The distribution of the CYP1A2 phenotype was previously investigated in our population by probit analysis, and a polymorphism was suggested (1). The ABP-Hb levels were different in rapid versus slow oxidizers depending on the level of smoking exposure. In fact, at low smoking exposure, rapid oxidizers showed the highest ABP-Hb levels, but at higher smoking exposure, slow oxidizers had the highest adduct levels. This difference might be due to pharmacokinetics in which the rate-limiting step in ABP metabolism changes with the dose in the different phenotypes. Interestingly, the trend of increasing ABP-Hb by NICO in rapid oxidizers seems to parallel the type of smoking and bladder cancer risk relationship suggested in studies that showed a leveling off of the dose-response curve at the highest doses (40–42).

Results on NAT2 (a noninducible enzyme) activity were also available. Slow acetylators exposed to carcinogenic amines are at increased bladder cancer risk due to their reduced detoxifying capacity (reviewed in Ref. 43). When the ABP-Hb levels were measured according to the combined NAT and N-oxidizer phenotypes, subjects with the rapid oxidizer-slow acetylator phenotype either had the highest adduct levels at a low dose of urinary NICO or were blond tobacco smokers. At increasing levels of smoking exposure, no major differences in adduct levels were found among the different combinations of phenotypes. This suggests that the excess risk entailed by carrying the at-risk phenotypes (slow NAT2-rapid CYP1A2) particularly affects people with low smoking exposure. At higher levels, the phenotypic trait is overwhelmed by the tobacco exposure. Other studies showed a similar pattern in the association between a susceptible genotype (i.e., the MspI, Ile-Val, and amino acid polymorphisms of the CYP1A1 gene) and the risk of lung cancer in subjects exposed to cigarette smoking (44–46). In these studies, individuals with the at-risk genotypes were at remarkably high risk of cancer at a low dose level of cigarette smoking, and the difference in susceptibility between genotypes was reduced at a high dose level. Moreover, subjects with the slow NAT2 phenotype and subjects with susceptible CYP2D6 and CYP2E1 genotypes have been associated with increased adduct levels at a low dose of smoking in other studies (8, 12).

We did not find an association between the GSTM1 genotype and ABP-Hb adduct levels. This finding is in contrast to what was recently shown (47), which suggested that GSTM1 is involved in the detoxification of 3- and 4-ABP. The small number of observations in our study is likely the reason for this discrepancy.

Our study showed that the cytochrome CYP1A2 phenotype can be induced by a variety of substances in tobacco smoke and in the diet. Further research on a larger scale is necessary to characterize these inducers. In addition, formal genetic studies supplemented by molecular investigations will be required to better understand the precise contribution of genetics to CYP1A2 activity. The finding of high ABP-Hb in rapid oxidizers, either in subjects with the combined rapid CYP1A2-slow NAT2 phenotype at low smoking exposure or with exposure to blond tobacco smoke (containing less aromatic amines than black tobacco smoke), needs particular attention. Low levels of exposure to aromatic amines in the environment, in fact, is widespread.

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References


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